What Is a NICE-SUGAR for Patients in the Intensive Care Unit?

The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact
                    Thomas Huxley, "Biogenesis and Abiogenesis"

A little more than 3 years ago, the editor-in-chief of *Mayo Clinic Proceedings* invited us to comment on the issue of glycemic control in critically ill patients.[1] The invitation stemmed from concerns related to the widespread adoption of intensive insulin therapy (IIT) after the publication of a seminal single-center trial (from Leuven, Belgium) in *The New England Journal of Medicine*.[2]

The trial concluded that "intensive insulin therapy to maintain blood glucose at or below 110 mg/dL reduces morbidity and mortality among critically ill patients in the surgical intensive care unit." In response to that article, hundreds, perhaps thousands, of intensive care units (ICUs) worldwide[3-12] began trying to implement IIT. Furthermore, this approach to glucose control was widely promoted by the Institute for Healthcare Improvement in its 100,000 Lives Campaign.[13]

The "tight glucose control express" seemed unstoppable. In the midst of such unfettered enthusiasm, we emphasized caution.[1] Perhaps because of our Australian and Japanese perspectives, we were able to view these developments with a degree of geographical and cultural distance and point out that the seminal study of IIT had a number of serious limitations.[2] First, it was not blinded, raising the possibility of bias. Second, most patients were recruited after cardiac surgery, raising concerns about the wider applicability of IIT to other populations.[14] Third, patients received intravenous glucose on arrival to the ICU at a dosage of 200 to 300 g/d (equivalent of 2 to 3 L of 10% glucose per day), an unusual practice.[4] Fourth, parenteral nutrition (PN), enteral feeding, or combined feeding was provided to all patients within 24 hours of ICU admission, also an unusual practice. Fifth, the mortality of patients who had undergone cardiac surgery in the control group was twice the national average for Australia, raising concerns about whether the control group was representative. Sixth, the unadjusted relative reduction in mortality was 42%, an effect exceeding that of any other interventional trial in critically ill or diabetic patients, stretching the biological plausibility of the findings.

At that time, we chose not to highlight even more sources of concern, such as the intrinsic limitations of single-center studies,[15] which make them unsuitable for level I evidence; the increased risk of hypoglycemia with IIT[2]; the potential medical Hawthorne effect of a protagonist investigator involved in the care of trial patients; and the nursing Hawthorne effect[15] associated with the extra attention provided to a patient assigned to IIT because of more frequent measurements of blood glucose. Additionally, we chose not to discuss the reverse nursing Hawthorne effect that, in the 1-nurse-to-2-patients Leuven ICU model of care, would occur when the nurse had to leave the bedside of a control patient to measure glucose in the nearby patient receiving IIT. Furthermore, we did not mention that, in an unblinded single-center study, the investigator is, de facto, performing a daily interim analysis for which no statistical correction is later applied or that independent data verification cannot occur. Finally, we did not highlight that, in single-center studies, unless multiple permuted blocks of randomization are used, the investigator has a better than even chance of guessing treatment allocation for the next patient. We thought that pointing out these methodological concerns would be seen as churlish in the midst of such therapeutic promise and widespread application.[14,10,16] Accordingly, we stuck to one simple message: We will wait for the results of the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) trial.[1]

Since then, the IIT tale has been characterized by a broad inability to reproduce the mortality benefits of the first trial. For example, in a subsequent trial of patients in a medical ICU in Leuven, IIT did not affect mortality.[17,18] In a large Belgian-French trial, no benefit was seen, and randomization was stopped because of concerns related to the high incidence of hypoglycemia.[19] The VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) study conducted in Germany met with the same fate.[20] A more recent study in Saudi Arabia confirmed this lack of benefit.[21] A recently published meta-analysis of all studies of IIT reached the inevitable conclusion that IIT does not decrease mortality but does increase the risk of hypoglycemia.[22] Predictably, debate has become fierce.[23]

In the meantime, we and others[14,24-27] continued to try to understand the association between glycemia and outcome and continued to raise concerns about IIT while asking clinicians to wait for the results of the NICE-SUGAR trial. The reasons for our pleas were obvious. NICE-SUGAR was designed to be a pivotal multicenter, multinational trial involving 42 hospitals in Australia, New Zealand, Canada, and the United States (US involvement was limited to a

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single center, Mayo Clinic). It was designed and conducted to the highest standards of trial medicine, with a reproducible Web-based protocol, the collection of almost 1 million glucose and insulin dose measurements, and patient follow-up to 90 days after randomization. With 6100 patients, the second largest randomized study sample (to our knowledge) in the history of critical care medicine, it would clearly provide level I evidence to guide clinicians in their decision making at the bedside. The results of the NICE-SUGAR trial have now been published,[28] and those clinicians who may have chosen to heed our advice 3 years ago are likely to feel gratified. The Mayo Clinic investigators are similarly likely to feel proud for contributing to this endeavor, instead of implementing IIT as many clamored for at the time. The NICE-SUGAR investigators found that, compared with conventional therapy (maintaining the glucose concentration at <180 mg/dL [to convert to mmol/L, multiply by 0.0555]), IIT was associated with an increased mortality 90 days after randomization. This occurred despite a much lower rate of hypoglycemia in the IIT group than reported in any previous studies of combined surgical and medical patients and with mean blood glucose levels clearly different in both groups, similar to that reported in the first IIT study. This detrimental IIT mortality effect in the NICE-SUGAR trial occurred in all subgroups, including surgical patients. As such, when considering a diverse population of ICU patients, the IIT express has surely come to its last stop. Yet, several questions will be asked: Why did the NICE-SUGAR trial show such a different outcome from the first Leuven study? Why and how did IIT cause increased mortality? How should we treat hyperglycemia in patients in the ICU? These and other questions are added to the list highlighted in the recent editorial in *The New England Journal of Medicine* that accompanied the NICE-SUGAR report.[29]

We think the first question is probably best asked in the reverse direction, given that the Leuven study of surgical patients has thus far been the only study to show a benefit for IIT in adults. Some will suggest that the use of PN in the Leuven study was responsible for the difference in outcome. Put another way, IIT "works," but only when patients receive most of their calories as PN, not when patients receive enteral nutrition. Others will suggest that some unique features of the Leuven protocol account for the discrepancy. We favor a simpler explanation as outlined previously: single-center studies are not robust representations of biological and/or clinical truth. The increase in mortality seen in the NICE-SUGAR trial most likely reflects greater statistical power and longer patient follow-up: the number of patients in the trial was almost 5 times more than that in any previous trial and patients were followed up for 90 days. Other trials may have found a

similar increase in mortality had they been of similar size and with longer patient follow-up. The results of a recently published meta-analysis[22] confirm that there is no benefit with IIT, but there is an increased risk of hypoglycemia. The mechanisms responsible for the increased mortality can be only a matter of speculation. Yet some of the trial findings (increased corticosteroid use and increased cardiovascular mortality with IIT) suggest a specific effect on blood pressure and circulation. Many experimental studies have demonstrated that both insulin and hypoglycemia can induce hypotension, vasodilatation, nitric oxide release, sympathetic system response exhaustion, and decreased ability to respond to repeated stress.[30-34] In addition, it has long been known that recent hypoglycemia can reduce autonomic responses and defenses against subsequent hypoglycemia.[33,34] These mechanisms may have played a major role in the differential outcomes in the NICE-SUGAR trial.

When considering the findings of NICE-SUGAR, it is also important to appreciate that it is unlikely that glycemic control is a "one size fits all" story. Subgroup analysis from the NICE-SUGAR trial already suggests heterogeneity in the response to glycemic control for patients with an operative admission to an ICU, in patients with trauma, and in patients receiving corticosteroids. Furthermore, diabetic patients[27] and patients with neurologic injury may represent specific subgroups in whom optimal glycemic control needs further definition.[35,36] With the NICE-SUGAR trial demonstrating that glycemic control affects survival, these concerns may be of more than pure academic interest.

Despite these caveats, we think it is important to emphasize that the findings of NICE-SUGAR do not justify neglecting glycemic control. Instead, we think that, whatever the mechanisms behind the findings of NICE-SUGAR, there is now a new and more moderate standard of care for glycemic management in the ICU: do not treat hyperglycemia unless the glucose level increases higher than 180 mg/dL; when you do treat hyperglycemia, aim for a target blood glucose concentration between 144 and 180 mg/dL. Until a study can provide level I evidence that a better approach exists, this should remain the standard of care. Such a standard of care also implies that, for example, in patients in the ICU, a glucose level of 243 mg/dL is just as undesirable as a glucose level of 80 mg/dL.

Finally, and this is vital, no matter what clinicians think might explain the findings of NICE-SUGAR, they should remember to be wary of the next single-center study that promises a simple solution for a complex problem. Single-center studies simply do not have the ability or resources to provide the type of scientifically rigorous analysis delivered by large multicenter, randomized controlled trials.[37-39] Waiting for level I evidence to emerge before adopting a

risky therapy is and will remain the best policy in clinical medicine for a long time.

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